dition of affairs is suggestive of the hypothesis that has been advanced that certain neoplasms may, in a tissue or organ, stimulate the parenchymatous cells to a sympathetic growth with the development of a new type of cell similar to that of the invading growth. Whether this can occur and whether there is in this an example of true metaplasia is questionable, and the exemplification found in this tumor is at most merely suggestive.

SPECIFIC IMMUNITY AND X-RAY THERAPEUTICS.[1]

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The medical mind believes in specifics, but distrusts a panacea. Quinine in malaria, mercury in syphilis, and iron in anemia are articles of faith in the therapeutic catechism. Diphtheria antitoxin cures diphtheria and nothing else. But the *x*-ray is put forth by its votaries as a treatment for a list of diseased conditions which are even less astounding for their number than for the wide diversity in their pathology and causes. However, the earnest testimony of many competent and reliable observers has compelled attention. But the question remains: How can a single agent be of service in such a bewildering variety of cases?

Some of the methods by which unaided nature is able to bring about recovery from infectious diseases have been disclosed and demonstrated in the last few years. We now understand that the presence of a minute quantity of infectious material within the body calls into play a wonderful set of protective processes. The blood serum is supplied with antibodies as various as the infectious agents, while the leukocytes, increasing in number and power, pour into the field, like an army of the interior, to engage in a life and death struggle with the invaders.

While the subject of antibodies is exceedingly complex, Wright has shown that the phagocytic power of the leukocyte, by which it is able to ingest and destroy bacteria, depends on certain antibodies in the serum which so injure the germs that they become an easy prey to the voracious white blood cell. He has called these antibodies opsonins. He also devised a method by which the blood serum, leukocytes, and any given bacteria may be brought in contact and kept at blood heat for fifteen minutes, after which cover glass preparations of the mixture can be stained and examined under the microscope. The average number of germs ingested per leukocyte, divided by the normal, gives the opsonic index.

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[1] Read at the annual meeting of the American Röntgen-ray Society, Cincinnati, October 4, 1907.

This opsonic index is an ascertainable factor in the natural specific immunity which follows recovery from an infectious disease. It also explains how an artificial immunity, no less specific, may be induced by hypodermatic injections, in proper doses, of the bacterial substance. The consideration of dosage is of importance in following the parallel which this paper indicates between opsonic and *x*-ray therapeutics. Too small a dose of bacterial substance fails to bring about a reaction. But it is truly astonishing to consider how small a proper dose is. 0.0025 mg. of the tubercle substance is the beginning dose. The protective forces of the body are delicately poised; otherwise they could not respond to such slight infections as may come through cuts and scratches, in time to prevent general infection. But, on the contrary, for the same reasons, too large a dose of bacterial substance overwhelms the immunizing forces of the system and plunges the patient into the so-called negative phase from which he may or may not recover. Doses must follow one another at right intervals, or else the reactions are cumulative and overwhelming on the one hand or isolated and ineffectual on the other. The proper dose and the correct interval can be ascertained only by repeated examinations of the blood. Clinical symptoms alone cannot furnish a guide, because the rise and fall of the opsonic index do not produce definite or uniform clinical symptoms.

Opsonic therapeutics has been conspicuously successful in certain diseases which have also been treated with equally conspicuous success by the *x*-rays. Examples of such diseases are lupus, acne, and glandular tuberculosis. In looking over the long list of diseases treated by the *x*-rays, it will be noticed that the large majority are either diseases known to be parasitic, or diseases running such a course that analogy compels us to believe in a microbic cause yet undiscovered. The antiseptic power of the *x*-rays being a negligible quantity, it has occurred simultaneously to many *x*-ray workers in various parts of the world, myself included, that the therapeutic properties of the rays might lie in some power to stimulate the production of opsonins in general in the body fluids. With this idea in mind, I made cultures from several pustules in a case of acne of the face about to be treated, and found that the infectious agent was the common Staphylococcus pyogenes albus. I then made an estimate of the patient's opsonic index to this germ, after which *x*-ray treatments were begun.

One observes from the chart of this case (Fig. 1) that the opsonic index was low before treatment, the average number of germs per leukocyte being 1 and the percentage of active leukocytes being 62.[2] An *x*-ray exposure of fifteen minutes at a distance of six inches was given. On the next day the average number of bacteria per leukocyte had risen to 1.42 and the active leukocytes to 70 per cent. On the third day the number of germs per cell had increased 300 per cent. and the number of active leukocytes had increased 17 per cent. Then, on the fourth day we found a slight fall, so that when the patient appeared on the fifth day, we gave a second treatment like the first, all parts except the affected area being, as usual, carefully screened by lead foil. On the day of this second treatment the average number of bacteria per leukocyte was 2.20, and the percentage of active leukocytes 70; but on the next day the figures were 3.18 and 92 per cent., and on the day following, which was the seventh day from the beginning treatment, the figures stood 5.20 and 96 per cent.; and on the eighth day, 8.70 and 100 per cent. of active leukocytes. On the ninth day the figures were 8.76 and 100 per cent., or an increase in phagocytic power of 876 per cent. over the beginning figure. The patient's face had completely cleared. Only brownish discolorations remained where the pustules had been. The patient had acquired, by some action of the *x*-rays, a specific immunity to Staphylococcus pyogenes albus.

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[2] All opsonic estimations were made with a serum dilution of 1 to 20.

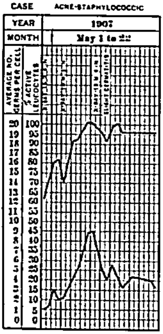


FIG. 1.—Upper curve = percentage of active leukocytes. Lower curve = average number of bacteria per cell.

On the tenth day, in obedience to an opsonic fall, we gave a third treatment. But there was no longer an acne to treat, and it is significant to note that the average number of bacteria per leukocyte declined to about 4 and the percentage of active leukocytes to about 96, where they remained as normal constants. The patient remains well up to date, and it is safe to predict that so long as his specific immunity endures he will be free from staphylococcic acne.

During the treatment of this case we made several estimations of the opsonic index to the tubercle bacillus, but we found that even at the height of the staphylococcic reaction the tuberculo-opsonic index remained unchanged.

The next case was one of lupus of the face, a small ulcer an inch in diameter on the temple (Fig. 2).

One observes a prompt rise after each treatment until the fourth, when there is a general decline until the seventh, when a rise again occurs. During this prolonged negative phase the lupus ulcer remained stationary, but with the upward swing of the opsonic index there occurred a rapid shrinking of the patch. With more experience on my part I could have regulated the *x*-ray dosage in more accurate accordance with the blood findings. As it was, the falling index restrained me from pushing the *x*-ray treatments as would usually be done when no dermatitis or skin reaction showed. Had the treatments been pushed, it is my opinion that the ulceration, which had been present ten years, would never have healed, but would have been classed as one of the inexplicable cases not amenable to *x*-ray treatment. After the fourth treatment I should have waited several weeks, if necessary, until some slight opsonic reaction occurred, and then, by smaller doses, should have nursed one small reaction after another, until a fair degree of immunity had been obtained. It is quite possible that in such cases we should

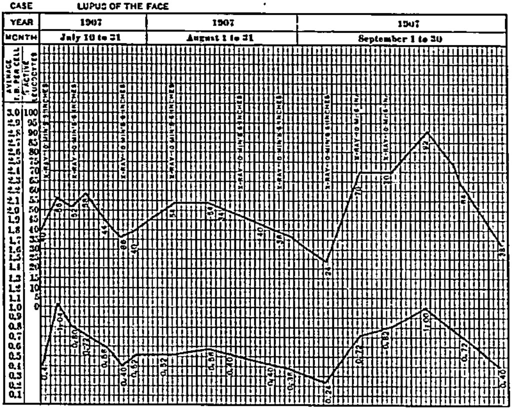
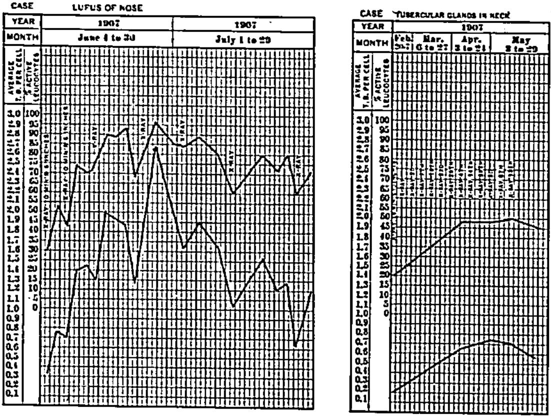


FIG. 2.—Upper curve = percentage of active leukocytes. Lower curve = average number of bacteria per cell.

be satisfied with a very moderate index, because, when the protective forces are feeble, the induction of high indices might easily lead to the exhaustion of the opsonin producing tissues, with the sudden relapse of the case, as *x*-ray operators sometimes see, without being able to furnish any adequate explanation.

The most striking case I have to offer is one of lupus of the nose. Seven *x*-ray treatments were given (Fig. 3). One sees that the tuberculo-opsonic index was low in the beginning. After each *x*-ray treatment there was a prompt jump in the index, until after the fourth treatment (twenty-two days from the beginning), the average number of tubercle bacilli per leukocyte had increased nearly seven and one-half times, and the active leukocytes had increased from 30 to 96 per cent. The lupus patch had healed, and from this time on the index gradually declined in spite of *x*-ray treatments.



FIGS. 3 and 4.—Upper curve = percentage of active leukocytes. Lower curve = average number of bacteria per cell.

Although I have been giving *x*-ray treatments from the first years of its employment as a therapeutic agent, I never before obtained such successful results with so few treatments and in so short a time. By analogy with our opsonic work I should attribute these results to the careful timing of the treatments. The opsonic estimations enabled us to give each treatment just as the positive phase began to decline.

The last case was one of tuberculous glands in the neck of a boy aged ten years. The patient had seven *x*-ray treatments before the opsonic estimations were begun (Fig. 4). One notices that the beginning figures are very low, but that under *x*-ray treatments a steady rise in the tuberculo-opsonic index is produced from February 20 until May 1, when a moderate fall occurs. By May 1, however, the glandular enlargements had disappeared, inasmuch as what was left were two very small, hard nodules representing the permanent remains familiar to *x*-ray therapeutists. The moderate degree of immunity obtained in this case is sufficient, and the patient remains free from tuberculosis.

In all these cases we see that the *x*-rays ceased to raise the index when the infectious agent was presumably eliminated; and furthermore that the index is raised only for germs present in the lesion. That is to say, the *x*-rays do not appear to stimulate the production of opsonins for bacteria in general, but only for those in living tissues brought directly under their influence. The charts of opsonic indices during *x*-ray treatments and the charts during opsonic vaccinations are similar in all essential particulars. The time of reaction after therapeutic application; the succession of negative and positive phases; the interval required between treatments, would seem to be too closely parallel to be accidental. The concomitant variations seem to prove a common cause; and the common cause seems to be the liberation, in the body fluids, of the immunizing substance of the disease-producing agent.

This is what is done in opsonic practice, and this is what the *x*-rays seem to do at the site of exposure. These principles, if they hold at all, will hold as well for cancer as for tuberculosis. In fact, if applicable, they must apply to all cases in which there is pathological material to which the body may react. Thus may we explain the tremendous negative phase which so often occurs after exposure of sarcoma to the *x*-rays. Equally well may we explain why we sometimes fail to cure in forty treatments the same sort of case that in another patient we cure in ten. That is to say, if our hypotheses are correct, we may, in one case, owing to the individual reaction from too frequent or too severe exposures, easily throw the patient into a succession of negative phases which prevent recovery. Or, in another case, we may fail, by too weak exposures, to liberate the immunizing substances; in which case frequency of exposures will not avail.

If I am permitted to draw conclusions from my limited data, I should suggest:

1. That all *x*-ray treatments, to be effectual, may require a degree of intensity sufficient to set free in the tissues what is equivalent to an autogenous vaccination.
2. That the duration of the exposure and the extent of the diseased tissue exposed should be so regulated as to induce either a small negative phase or none at all.

3. That the repetition of exposures, as far as possible, should be governed by the duration of the negative and positive phases; and that in diseases of which the disease-producing agent is as yet undetermined, one should be governed by analogy with those cases in which opsonic estimations can be made.

It follows as a corollary that it is not necessary to expose the whole area in order to bring about complete recovery, and that exposure should not, as a rule, be repeated oftener than twice a week, and probably usually at less frequent intervals, to get the maximum results and to avoid prolonged or incurable negative phases. It is also increasingly necessary to measure our *x*-ray dosage. In this respect *x*-ray therapeutics is lacking in precision. No method has yet been made practicable by which we may exactly specify the quality and quantity of the *x*-ray dose.

The advantage of *x*-ray treatments over opsonic therapeutics is considerable:

1. The immunizing substance set free under the influence of the *x*-rays is of necessity autogenous; that is, it is formed from the actual microbic strain which is producing the disease. One has only to read Wright's articles to learn how important it is in opsonic practice to use a vaccine made of the bacteria from the patient rather than from a stock culture.
2. Many of the difficulties and mistakes incident to a bacteriological diagnosis are eliminated.
3. In cases in which the bacteriological cause is as yet undetermined, or in which the disease-producing agents are not bacteria, the *x*-rays are nevertheless applicable.

In conclusion, I must state I am well aware that I have carried my deductions and conclusions far beyond the limits warranted by the number of cases I have to report. My excuse is, to set the subject, along with obvious hypotheses, squarely before the profession, in the hope that other workers may be invited into what has seemed to me a fertile field of therapeutic endeavor.